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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/469,637	12/22/1999	MARSHA A. MOSES	CMZ-083CPCN	5202

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EXAMINER
GITOMER, RALPH J

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/469,637	Moses et al.
Examiner	**Art Unit**
Ralph Gitomer	1651

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Jun 16, 2003.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 130-162 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 130-162 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 24
4) ☒ Interview Summary (PTO-413) Paper No(s). 26
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

The amendment and IDS received 6/16/03 have been entered and claims 130-162 are currently pending in this application. This Office Action is made non-final because the claims are now in condition for searching and art is applied as follows. Please update the specification regarding related applications. The new abstract must be submitted on a separate page. There may be a typo in the specification on page 32, line 21. Priority is claimed to 4/26/1996 which is a CIP. Please inform the examiner as to how the parent application differs from the CIP to determine the proper priority date.

It is noted the IDS received 2/23/2000 has not been considered because the references are not found in the file. And all the references found in the IDS received 6/16/2003 are published after the claimed priority date.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 130-162 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,037,138. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims encompass those of `138.

Claims 130-162 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while possibly being enabling for specific enzymes and prostate cancer detected by specific MMP's, does not reasonably provide enablement for "a matrix metalloproteinase" or "cancer". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is noted present claims 134-148 are directed to various cancers such as any epithelial, mesodermal, endodermal, hematopoietic origin, retina, skin, renal and lymphoma in general, and other claims include other tissues, but no such types of cancer of such tissues are enabled by the present specification.

In claim 130 and all occurrences, "cancer" and ▒a matrix metalloproteinase▒ lack enablement as it would require one of ordinary skill in this art undue experimentation to determine which such cancer or proteinase would work in the instant invention. Note that a given organ, for example the kidney, is prone to more than one type of cancer. Also, regarding the claims directed to ▒an MMP▒, it appears in the Tables in the present specification that not all gelatinases are effective in the claimed invention, only possibly two may be and they are not characterized in any meaningful way.

▒A matrix metalloproteinase▒ reads on a multitude of Calpains among many other enzymes which are unlikely to work in the claimed invention.

"Cancer" reads on basal cell carcinoma to Ewings sarcoma which are unlikely to work in the claimed invention.

The entire scope of the claims has not been enabled because:

1. Quantity of experimentation necessary would be undue because of the large proportion of inoperative disorders and compounds claimed.

2. Amount of direction or guidance presented is insufficient to predict which disorders and substances encompassed by the claims would work.

3. Presence of working examples are only for specific disorders and substances and extension to other disorders and compounds has not been specifically taught or suggested.

4. The nature of the invention is complex and unpredictable.

5. State of the prior art indicates that most related disorders and substances are not effective for the claimed functions.

6. Level of predictability of the art is very unpredictable.

7. Breadth of the claims encompasses an innumerable number of disorders and compounds.

8. The level of one of ordinary skill in this art is variable.

In re Wands, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

Applicant's arguments filed 9/26/02 have been fully considered but they are not persuasive.

Applicants argue that The Table 3 on page 22 shows various forms of cancer can be detected by the claimed method. And the specification enables specific enzymes, cancers, MMP's and cancers.

It is the examiner's position that Table 3 indicates that bladder, renal, lymphoma, testicular, and pheochromocytoma cannot be detected by the claimed method. In Table 2 on page 21 subjects with prostate cancer had either or both the presence of >150 kDa or 92kDa enzymes of some sort to some extent. No controls are seen. In Table 3 it wold appear rather random if the subjects had either or both of the same enzymes, no predictability is seen. And there are no controls shown in Table 3 either so no statistical significance can be determined.

The specification broadly mentions classes of enzymes, cancers, MMP's and cancers and does possibly provide enablement for the claimed invention for specific subsets of the above, but does not provide how to make and use the invention as claimed.

Claims 130-162 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Each of the following applies in all occurrences.

There are many instances of lack of antecedent basis in the claims, claim 130 line 1, ▒the diagnosis▒, line 6, ▒the presence▒ and many other occurrences. In claim 1 line 3, ▒a subject▒ does not related to the preamble subject. In claim 130, it is not seen what the correlation may be between the presence or absence of MMP with cancer. The preamble of claim 131 is unclear as to monitoring prognosis and monitoring diagnosis. Claim 131 is based upon using a marker but it does not recite how it is used. In claim 150 there is lack of antecedent basis for ▒the detection step▒. There may be a typo in claim 156. It is noted that the present claims are limited to detecting the presence or absence of any MMP in urine, not any quantity of MMP.

As discussed in the interviews, the claims have now been limited to determining a urine sample only.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 130-131, 134-136, 143, 146, 147 are rejected under 35 U.S.C. 102(b) as being anticipated by Ueda.

Ueda (Nippon Hinyokika Gakkai Zasshi) entitled "A Study on Cathepsin B Like Substance in Patients with Urological Cancer" teaches in the abstract, cathepsin B, a cysteine proteinase was determined in urine and was higher in those subjects with carcinoma than in controls. Renal, bladder, and ureter carcinoma are specifically taught.

Claims 130-131, 134, 146, 150, 154-155, 158-160, 162 are rejected under 35 U.S.C. 102(b) as being anticipated by Margulies.

Margulies (Cancer Epidemiology Biomarkers & Prevention) entitled "Urinary Type IV Collagenase: Elevated Levels Are Associated with Bladder Transitional Cell Carcinoma" teaches in the abstract, the amount of collagenase was significantly elevated in the urine of carcinoma subjects compared to normal controls. This may be a useful marker for cancer diagnosis or prognosis. Bladder carcinoma is specifically taught. Methods of determination include enzyme linked immunosorbent assay, Western immunoblotting, and gelatin zymography. On page 468 column 2, urine samples were concentrated prior to testing.

Claims 130-131, 136, 146 are rejected under 35 U.S.C. 102(a) as being anticipated by Guolan.

Guolan (Huaxi Yike Daxue Xuebao) entitled "The Value of Urine Cysteine Proteinase and Serum CA125 Measurement in Monitoring the Treatment of Malignant Ovarian Tumor" teaches in the abstract, urine cysteine proteinase was significantly higher in subjects with malignancies than controls.

Claims 130-131, 136, 144, 146 are rejected under 35 U.S.C. 102(b) as being anticipated by Okubo.

Okubo (JP 4-110660) entitled "Reagent for Liver Disease Diagnosis" teaches in the abstract, determining calpains in urine to diagnose hepatic carcinoma.

Claims 130-137, 139, 142, 146-148, 160, 162 are rejected under 35 U.S.C. 102(a) as being anticipated by Brunner.

Brunner (6,224,865) with a publication date of January 26, 1995, entitled ▒Supression of Inhibitors▒ teaches in column 8, matrix degrading enzymes are described. For a number of types of malignancies, e.g. mammary cancer, an increased concentration of the matrix degrading enzyme has been established to be a prognostic factor indicating a poor prognosis for the patient having the malignancy. In column 9, lines 37-51, malignancy types include mammary, urological, prostate, bladder, gynacological, GI, gastric, hematological, lymphoma, skin. In column 10 line 3, urine samples are specified.

All the featues of the claims are taught by the above references for the same function as claimed.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 132-133, 138-142, 145, 148-149, 151-153, 156, 157, 161 are rejected under 35 U.S.C. 103(a) as being unpatentable over each of Ueda, Margulies, Guolan and Okubo.

The claims differ from the above references in that claims 132-133 are directed to prostate cancer specifically, claims 138-142, 145, 148 are directed to cancer of the nervous system, breast cancer, retina cancer, lung cancer, skin cancer, pancreatic cancer, and lymphoma, specifically. Claim 149 is directed to a proenzyme, claim 151 is directed to the urine being dialyzed, claims 152-153 are directed to the subject has previously been treated surgically or hormonally, claims 156-157 are directed to the MW of the proteinase and claim 161 is directed to a radioimmune assay.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to detect any desired type of cancer in view of the above references which teach a large variety of cancers are detected by the presently claimed method. It is known that many different cancers are associated with the presently claimed class of enzymes and to detect larger than normal amounts of the enzyme to detect the cancers shown by the references to then detect other cancers also known to be associated with the same enzymes would have been obvious.

Regarding claim 149 directed to a proenzyme, the chemistry of MMP's is well known and to detect any of the closely related compounds known to be associated with MMP's for the function of detecting MMP's would have been obvious.

Regarding claim 151 directed to the urine being dialyzed, to treat a sample prior to determining is well known in this art and various sample treatments are shown in the references.

Regarding claims 152-153 directed to previous treatment of the subject, the cited references appear to be silent concerning any treatment administered prior to the determination. However, the studies are directed to subjects who are already aware of their having cancer so it would seem likely that many have also been treated for the condition.

Regarding claims 156-157 directed to the MW of the proteinase, the above cited references do not all recite the MW of the enzymes detected. However, the references teach the same

types of enzymes as claimed for the same function and it would appear likely that they are within the ranges presently claimed.

Regarding claim 161 directed to a radioimmune assay, the references teach a variety of types of assays and radioimmune assays for enzymes are well known in this art and would have the expected result. To apply any known type of assay for its known function with the expected result is not novel.

The following prior art pertinent to applicant's disclosure is made of record and not relied upon:

Aoki (Biol Pharm bull) teaches determining gastric cancer proteinase in urine.

Mikulewicz (AntiCancer Drugs) entitled "Decrease in vivo of Cysteine Endopeptidases in Blood of Patients with Tumor of the Larynx" teaches on page 343 column 1, the urine of patients with neoplastic diseases have increased levels of cysteine peptidase inhibitors.

Green (6,544,761) teaches metalloproteinases.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ralph Gitomer whose telephone number is (703) 308-0732. The examiner can normally be reached on Tuesday-Friday from 8:00 am - 5:00 pm. The examiner can also be reached on alternate Mondays. If attempts to reach the examiner by telephone are unsuccessful, the

examiner's supervisor, Michael Wityshyn can be reached on (703) 308-4743. The fax phone number for this Art Unit is (703) 308-4556. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235. For 24 hour access to patent application information 7 days per week, or for filing applications electronically, please visit our website at www.uspto.gov and click on the button "Patent Electronic Business Center" for more information.

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